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Department of Health and Human Services

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Food and Drug Administration

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21 CFR Part 201

Specific Requirements on Content and Format of Labeling for Human  
Prescription Drugs; Revision of ``Pediatric Use'' Subsection in the  
Labeling; Final Rule

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 92N-0165]

Specific Requirements on Content and Format of Labeling for Human  
Prescription Drugs; Revision of ``Pediatric Use'' Subsection In the  
Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

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SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format on labeling for human prescription drug products. The final rule revises the current ``Pediatric use'' subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more complete information about the use of a Drug in the pediatric population (ages birth to 16 years). The final rule, which applies to prescription Drug products (including biological prescription Drug products), recognizes several methods of establishing substantial evidence to support

pediatric labeling claims, including relying, in certain cases, on studies carried out in adults. This final rule also requires that if there is not substantial evidence to support any pediatric use or use in a particular pediatric population, the labeling shall state this. Sponsors must reexamine existing data to determine whether the ``Pediatric use'' subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new Sec. 201.57(f)(9)(iv) by December 13, 1996. This action responds to concerns in FDA and elsewhere that current prescription Drug labeling often does not contain adequate information about the use of drugs in the pediatric population. This action promotes safer and more effective use of prescription drugs in the pediatric population.

DATES: Effective January 12, 1995. The agency will accept ``pediatric use'' information based on revised Sec. 201.57(f)(9) (21 CFR 201.57(f)(9)) after January 12, 1995. Sponsors must reexamine existing data, and, if appropriate, submit a supplemental application to comply with new Sec. 201.57(f)(9)(iv) by December 13, 1996.

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#### SUPPLEMENTARY INFORMATION:

##### I. Background

In the Federal Register of October 16, 1992 (57 FR 47423), FDA proposed to amend its regulations pertaining to the content and format of prescription Drug labeling in Sec. 201.57 by revising the current ``Pediatric use'' subsection (Sec. 201.57(f)(9)) to allow a broader basis for the inclusion of information about use of a Drug in the pediatric population. The proposal would have allowed pediatric claims based not only on adequate and well-controlled studies in the pediatric population but also, in some cases, on such trials in adults. The proposed regulation described other data needed when pediatric claims are based on trials in adults and indicated specific labeling language and the location of various kinds of information.

FDA issued the current pediatric labeling requirements in 1979 (44 FR 37434, June 26, 1979). The current regulation, codified at Sec. 201.57(f)(9), requires that specific pediatric indications, if any, be described under the ``Indications and Usage'' section of the labeling, with appropriate pediatric dosage provided under the ``Dosage and Administration'' section. The current regulation also requires that recommendations for pediatric use be based on substantial evidence derived from adequate and well-controlled studies in the pediatric population, unless that requirement is waived. If a Drug's safety and effectiveness in the pediatric population cannot be established or if the Drug's use in the pediatric population is associated with a specific hazard, the current regulation requires appropriate statements or details.

By establishing a ``Pediatric use'' subsection and describing its content and format, the 1979 regulation was intended to encourage Drug labeling that would regularly provide adequate information about use of prescription drugs in pediatric patients. As stated in the preamble to the proposed rule on which this final rule is based, however, most prescription Drug products still lack adequate information about their use in pediatric populations. For example, an informal survey done in 1990 by the American Academy of Pediatrics examined labeling of all new molecular entities approved between 1984 and 1989 and found that 80 percent had no information on pediatric use. Other surveys have shown that the labeling for many prescription drugs states that safety and effectiveness in children have not been established and contains no information on pediatric use, even for drugs that are commonly prescribed for pediatric patients.

FDA continues to be concerned that, without adequate information,

practitioners may be reluctant to prescribe certain drugs for their pediatric patients, or may prescribe them inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.

The continuing absence of pediatric use information in prescription Drug labeling may be due in part to the impression, perhaps conveyed by the existing regulation, that pediatric claims must always be based on adequate and well-controlled studies conducted in the pediatric population. Given the many problems associated with the testing of drugs in the pediatric population (e.g., obtaining informed consent for tests not directly of benefit to the child, use of placebo controls in a vulnerable population), studies meeting this standard are often difficult to obtain. Existing FDA regulations do not, in fact, require that controlled trials always be conducted in the pediatric population to support a pediatric use. Under current Sec. 201.57(f)(9), the need for such studies may be waived where other data can satisfy the requirements of law. The basis for granting such a waiver is not, however, clear in the existing regulation. Section 201.57(f)(9)(iv) of this final rule clarifies how the agency will determine that data from adequate and well-controlled studies with adult subjects can provide substantial evidence of effectiveness in the pediatric population.

In summary, this rule is intended to provide practitioners with more pediatric use information in the labeling of human prescription Drug products so that practitioners will have more reliable information upon which to base a decision to prescribe a Drug for use in their pediatric patients. The rule does this by encouraging manufacturers to provide more information on Drug labels upon which practitioners can base their decisions. The rule does not, however, limit the manner in which a practitioner may prescribe an approved Drug.

## II. Highlights of the Final Rule

The final rule revises the current ``Pediatric use'' subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more comprehensive information about use of a Drug in the pediatric population. Under the final rule, products may be labeled for pediatric use based on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data). Such reliance on studies in adults was possible under the waiver provision in the existing rule, but the waiver provision was not often used. Of course, products may also be labeled for pediatric use based on adequate and well-controlled studies in the pediatric population. The pediatric age group, birth to 16 years, includes pediatric age groups often called neonates, infants, children, and adolescents. In the final rule, because the term ``children'' can be interpreted as referring only to a particular subset of the pediatric population (ages 2 to 12 years), and to make clear that the provisions of this rule apply to the entire pediatric population, references to ``children'' in the proposed rule have been deleted and replaced by ``pediatric population'' or ``pediatric patients.''

The major provisions of the final rule are summarized as follows:

The final rule continues to permit a specific pediatric indication (i.e., an indication different from those approved in adults) supported by adequate and well-controlled studies in the appropriate pediatric population, to be described under the ``Indications and Usage'' section of the labeling, with the appropriate pediatric dosage given under the ``Dosage and Administration'' section of the labeling. The ``Pediatric use'' subsection of the labeling must include any limitations on the pediatric indication, need for specific monitoring, specific hazards of the Drug, differences between pediatric and adult responses to the Drug, and other information related to the safe and effective use of the Drug in pediatric patients.

If there are specific statements on pediatric use of the Drug for

an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section of the labeling. This subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the Drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the Drug, and other information related to the safe and effective pediatric use of the Drug.

A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the Drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.

Where the requirements for a finding of substantial evidence to support a specific pediatric indication or a pediatric use statement have not been met for a particular pediatric subgroup, the "Pediatric use" subsection of the labeling must contain a statement that appropriately characterizes the limitation, such as "Safety and effectiveness in pediatric patients [below the age of (--) (years/months/weeks)] have not been established." If use of the Drug is associated with a specific hazard in this pediatric subgroup, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Where the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, the "Pediatric use" subsection of the labeling must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the Drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Any sponsor who believes that no "Pediatric use" subsection is appropriate or relevant to the labeling of its particular Drug product must provide FDA with reasons justifying its omission, and may propose alternative statement(s).

Finally, recognizing the hazards that inactive ingredients can pose to the pediatric population, the final rule requires that prescription Drug labeling contain statements about inactive ingredients that might be toxic to the neonate or other pediatric subgroup.

### III. General Comments on the Proposed Rule

FDA received 11 comments on the proposed rule from prescription Drug manufacturers, prescribers, professional societies, organizations with special interests in the pediatric population, the lay public, and others. Most supported the proposed labeling change, calling it "timely and important," "an important \* \* \* step to facilitate the inclusion of information about use of drugs in children in the approved labeling," "a significant step toward the goal of including infants and children in the Drug approval process," and a way "to fill the gap of information that currently exists in the area of appropriate Drug usage in children."

One comment, for example, stated that providing pediatric use information in labeling will help health professionals reach rational Drug therapy decisions for pediatric patients. The comment added "any information that can be used by pharmacists to assure rational Drug

therapy in special populations will be a positive addition to Drug information. \* \* \* Such labeling will enhance the likelihood of positive outcomes in pediatric patients.'

However, some comments were less supportive, including one that stated: ``While \* \* \* [we] commend the FDA on its initiatives to improve information available to physicians and their pediatric patients regarding prescription Drug use, we remain concerned that this approach will not measurably assist physicians.'

Most comments also raised specific issues for consideration by the agency. These issues are described below.

#### A. Definition of ``Pediatric''

1. Several comments suggested that age breakdowns within the pediatric population might be appropriate. The pediatric age range begins at birth, and may cover individuals as old as 18 years to 21 years, encompassing the subspecialties of neonatology and adolescent medicine. One comment suggested that the rule define ``pediatric'' as children under 12 years, because ``it has been commonly accepted that ages 12 years to 18 years may be included without previous clinical work in that age group.' The comment also suggested that the rule state the age group when pharmacokinetic studies should be done in order to extrapolate the results from infancy through adolescence, or state whether the age range will be broken into subgroups with testing required for each. Another comment said that a definition of ``pediatric'' would have to consider Drug metabolism, pharmacokinetics, and interaction with various organs and other body systems. The comment suggested that a system by which distinct classes of drugs are considered differently may be more logical and appropriate.

Another comment noted that pediatric patients are not homogeneous, and that age groups show significant differences in functional and physiological functions. The comment suggested that information from clinical studies be subdivided by age groups and their respective responses to drugs, suggesting age categories of premature infant, newborn, children under 2 years of age, children 2 years to 13 years, and adolescents 13 years to 18 years.

Another comment said that individuals 16 years to 18 years of age pose particular problems and suggested consultation with the American Academy of Pediatrics' Committee on Drugs to consider defining age categories or groups for pediatric labeling.

The ``Pediatric use'' subsection of labeling is where information about use of a Drug in pediatric patients is located, and Sec. 201.57(f)(9) describes in general terms the kind of information that should be included. The ``Pediatric use'' subsection does not attempt to resolve the many difficult issues related to use of drugs in this population. What appears in this subsection (e.g., age groups covered) will depend on the data available, and the ability to define results for specific subgroups. As a general matter, however, the agency offers the following guidance and useful breakdowns. The following age categories for the pediatric population are commonly distinguished, although the distinctions are inevitably arbitrary: (1) Birth up to 1 month (neonates), (2) 1 month up to 2 years of age (infants), (3) 2 years up to 12 years (children), and (4) 12 years up to 16 years (adolescents). Where possible, data should be analyzed by these groups, but it should not usually be necessary to establish a Drug product's effectiveness in each group. It may, on the other hand, be important to have some pharmacokinetic information in each group, especially the younger age groups, to guide dosing and additional information, such as a specific study in neonates, to establish safety.

Although the agency has determined that the term ``pediatric patients'' refers to individuals from birth to 16 years of age, the agency recognizes that for some drugs, adult studies may be applicable to pediatric patients under the age of 16 years who have passed puberty; indeed, a primary purpose of this rule is to allow pediatric labeling based on adult studies, when appropriate. Although in many cases, additional pharmacokinetic and safety data may be needed to support pediatric use statements, in other cases, particularly for pediatric patients in the 12-to 16-year age group, there may be less

additional data needed.

#### B. Applicability of the Rule to Biological Drug Products

2. One comment said that it was unclear whether the rule applies to biological Drug products.

The rule (as well as Sec. 201.57 in general) applies to biological Drug products.

#### C. Pediatric Studies

3. One comment noted that about 80 percent of Drug labeling currently contains language excluding use of the Drug in pediatric patients or limiting use only to specific age groups. The comment asked FDA to encourage sponsors to include pediatric patients in their clinical studies when the Drug is likely to be effective for an indication in this population.

As stated in the preamble to the proposed rule, FDA encourages sponsors to include pediatric patients in their clinical studies, and analyzes investigational new Drug applications and new Drug applications (NDA's) to determine whether studies in this population should be done before the Drug is approved (57 FR 47423 at 47424). Under certain circumstances, the agency may require that clinical studies in the pediatric population be conducted before marketing approval (see response to comment number 4 in section III.C. of this document). If a Drug is likely to be effective for pediatric use, the agency is making it clear that labeling for pediatric use may sometimes be based on adequate and well-controlled studies in adults, with additional pediatric data. FDA intends that this rule will call further attention to the need for creating and reviewing data on pediatric use.

4. One comment asked whether FDA intended to require a sponsor to submit information for a specific pediatric indication or use if there are available data suggesting that such an indication or use would be permitted under the regulation. The comment said that there may be "good reasons" why a sponsor might not wish to seek a pediatric indication or use for a Drug even when available evidence would support such a use. For example, the Drug's benefit/risk ratio in the pediatric population might be different from that in adults, or there might be sufficient and better alternative therapies available for the pediatric use. Additionally, the comment expressed concern that a Drug that has been tested in adults may not provide a sufficient legal defense against a claim for injury of a child. The comment said that a sponsor should not be forced to assume or be placed in the position of having to defend such an action unless the sponsor believes the data in support of the pediatric use are sufficient, and that a sponsor should not be mandated or forced by the rule to seek a pediatric use if the sponsor, for whatever reason, does not wish to do so.

Another comment expressed concern that FDA might delay approval of products that have good existing available data for safety and efficacy in adults while acceptable pediatric information is developed.

This rule does not add a new requirement that sponsors carry out new pediatric studies, nor does it require that sponsors submit labeling with claims that are inadequately supported. New Sec. 201.57(f)(9)(iv) provides that a pediatric use statement may be based on adequate and well-controlled studies in adults, provided that the course of the disease and the Drug effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Sponsors are required to reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if safety and effectiveness for pediatric use have been demonstrated, submit a supplemental application to comply with new Sec. 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and Drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under this provision. Under new Sec. 201.57(f)(9)(vi),

the sponsor may propose labeling stating that safety and effectiveness in pediatric patients have not been established.

Additionally, under new Sec. 201.57(f)(9)(vii), if the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of that section is appropriate or relevant to the labeling of a particular Drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). In response to such a proposal, FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the Drug's labeling and that the alternative statement is accurate and appropriate. Section 201.57(f)(9)(vii) has been modified to make this explicit.

Although this rule does not add new requirements for conducting pediatric studies, various provisions of the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS act), and existing regulations authorize FDA to require such studies under certain circumstances.

Under section 505(k) of the act (21 U.S.C. 355(k)), FDA may require NDA holders to establish records and submit reports to the agency on data relating to clinical experience or other data or information in order to determine whether there may be grounds for revoking the NDA approval. Such a requirement may be established either through regulation or through an order regarding the NDA (21 U.S.C. 355(k)(1)).

Existing regulations require application holders to report to the agency adverse experiences occurring in the course of use of the product in professional practice, as well as during clinical investigations (21 CFR 312.32, 314.80). In addition, approved application holders must submit as part of the annual report a summary of significant new information that might affect the safety, effectiveness, or labeling of the product, as well as copies of unpublished and published reports of studies of the Drug (21 CFR 314.81(b)(2)(i), (b)(2)(v), and (b)(2)(vi)). The report also must contain a description of the action the company has taken or intends to take because of the new information, such as submission of a supplement, addition of a warning, or initiation of a new study (21 CFR 314.81(b)(2)(i)).

Section 505(e) of the act specifies grounds on which the agency may withdraw or suspend approval of an NDA. If there is an imminent hazard to the public health, approval of the NDA may be suspended immediately by the Secretary of the Department of Health and Human Services. In addition to other circumstances, approval of an NDA is to be withdrawn if clinical experience or other data show that the product is unsafe or not shown to be safe under the conditions of use upon the basis of which the application was approved. Moreover, the approval may be withdrawn if the labeling is false or misleading and not corrected within a reasonable time after notice of the matter.

Under section 502(a) of the act (21 U.S.C. 352(a)), a Drug is considered misbranded if its labeling is false or misleading. Section 201(n) of the act (21 U.S.C. 321(n)) makes it clear that the "misleading" determination is to be based not only on representations made or suggested in the labeling, but also on failure to reveal material facts. Material facts include those which concern consequences which may result from use of the product under the labeled conditions of use or under customary or usual conditions of use. These conditions of use may include off-label uses prescribed by practitioners for their patients.

In addition, drugs are considered misbranded under section 502(f) of the act if the labeling fails to bear adequate directions for use. FDA regulations define adequate directions for use as directions under which the lay person can use a Drug safely and for the purposes for which it is intended (21 CFR 201.5). "Intended uses" are further defined in the regulations to include uses other than the ones on the labeling (21 CFR 201.128). If a manufacturer knows that a Drug is used for an off-label use, the manufacturer may be required to provide adequate labeling for that use (21 CFR 201.128).

Prescription drugs for human use are exempt from the requirement to carry adequate directions for lay use under certain circumstances, if labeled with the prescription legend (21 CFR 201.100). Among the

exemption criteria is the requirement that the Drug carry adequate labeling for the prescriber, as authorized by an approved application, for the intended use. In summary, the Drug product is misbranded if the intended use is not approved in an NDA.

Drug products are also misbranded, under section 502(f)(2) of the act, if the labeling does not carry adequate warnings against unsafe use. Such unsafe use may include use by pediatric patients where the use may be dangerous to their health, or unsafe dosage or methods or duration of administration in the pediatric population.

Biological Drug products are approved under authority of section 351 of the PHS act (42 U.S.C. 262). This provision authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products (42 U.S.C. 262(d)(1)). An approved product license application (PLA) may be revoked if the product does not conform to applicable requirements in the regulations or is not safe and effective for all of its intended uses or is misbranded with respect to any such use (21 CFR 601.5(b)(4) through (b)(6)). If there is a danger to health, the Commissioner may suspend the product license (21 CFR 601.6). Under section 351(b) of the PHS act, no one may falsely label a biological product. Biological Drug products are also subject to the applicable Drug provisions of the Federal Food, Drug, and Cosmetic Act, as previously discussed.

Moreover, the agency has stated that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a Drug once it is marketed (58 FR 39406 at 39409, July 22, 1993). This conclusion, stated explicitly in a guideline on the need for data in both genders, applies equally to age subgroups, including pediatric and geriatric populations. FDA may refuse to approve an application that fails to contain sufficient information to determine whether the product can be safely and effectively used in populations likely to receive it. In addition, for an approved Drug, in certain cases (e.g., where the Drug is widely used, represents a potential hazard, or is therapeutically important in pediatric patients), FDA may require further studies in pediatric populations and appropriate labeling changes. As previously discussed, an already approved Drug may be considered illegally marketed if adequate information on safe and effective use in pediatric patients is not obtained and included in the labeling.

The agency thus expects sponsors to seek supplemental claims for pediatric uses that are supported by adequate data. This does not imply, however, that a sponsor should seek a claim for a pediatric use if the benefits of that use do not outweigh its risks; the determination of whether to include a pediatric use statement must be based on clinical data, and other use information, not on a vague concern about liability.

5. One comment said that although the desire to use potentially relevant data in the "Pediatric use" subsection of the labeling was "understandable," such data should not take the place of adequate and well-designed controlled studies in the pediatric population, and that FDA ultimately may have to require such studies. The comment stated that FDA should require manufacturers to fund research projects regarding Drug safety and efficacy, including short-term and long-term side effects, in pediatric patients.

FDA agrees that clinical studies regarding a Drug's safety and effectiveness in pediatric patients are desirable, and the agency encourages such studies in appropriate cases. As discussed in comment 4 in section III.C. of this document, the agency has the authority to require such studies under certain circumstances. In some cases, such studies may be required prior to approval where pediatric use is important and where the adult and pediatric diseases cannot be considered sufficiently similar. In other cases, the controlled trials in adults, with pharmacokinetic and other data as needed, may support valid pediatric labeling.

6. One comment stated that FDA should consider other alternatives to the rule, including a formal review process that collects and analyzes available safety and efficacy data on a Drug's use in the pediatric population both before and after marketing approval, which, through committee review, could recommend further testing of the Drug



after it is marketed if specific pediatric safety or efficacy concerns are found.

FDA believes that the comment has misinterpreted the purpose of the rule. The rule describes the kind of data and information that can be included in labeling for the pediatric population. In general, it is the sponsor's responsibility to collect, on a continuing basis, available data on safety and efficacy, propose revised labeling, and carry out needed studies. In some circumstances, FDA has required pediatric studies prior to approval, elicited agreement by Drug sponsors at the time of marketing approval to carry out additional pediatric studies after approval, or stimulated conduct of pediatric studies after approval. When appropriate, FDA makes use of its standing advisory committees to help decide whether and when pediatric studies are needed.

7. One comment stated that FDA should revise the rule to specify what data must be provided by manufacturers. The comment asked what number of pediatric patients would be sufficient to determine if there is a difference in age-related response, and how FDA will determine that all available information about the pediatric use of all available drugs has been included, including epidemiologic studies.

FDA declines to accept the comment's suggestion. The agency believes that specifying an exact number of pediatric patients to be studied would be impractical due to variations in the pediatric population and responses to different drugs. This is particularly true, given the various kinds of data that can be used under the rule to support pediatric labeling.

#### D. Drugs Currently Under Review

8. One comment suggested that drugs currently under development or under review by FDA should be given special consideration to avoid delays in development and approval associated with implementation of the rule.

FDA does not expect delays in review or approval as a result of this rule. FDA already examines available pediatric data under current labeling regulations. The principal change created by the revised regulation is the ability to rely on studies in adults to support pediatric efficacy in some situations.

#### E. Supplements for Drugs Already Approved

9. One comment suggested that FDA work with manufacturers of approved drugs to develop a method that allows the manufacturers to update their labeling in a quick and cost-effective manner. The comment also said that package inserts do not generally reflect current scientific literature because of the problems with current methods of updating labeling. The comment said that this had created situations where prescribers are making decisions on treatment modalities without the benefit of timely information.

FDA does not believe that changes in regulations are needed to allow timely updating of labeling. Under the current regulations, applicants can propose changes in their approved labeling. FDA normally reviews supplements subject to prior approval in the order received. Effectiveness supplements are rated as priority or standard and are subject to performance goals set in connection with the Prescription Drug User Fee Act of 1992.

10. One comment said that the filing and approval of pediatric labeling supplements from different sponsors on different timetables could mean that some labels for products considered to be substantially similar might be silent with regard to pediatric usage, while others might be detailed. The comment suggested that FDA and the American Academy of Pediatrics' Committee on Drugs could identify therapeutic classes to be relabeled first, so that FDA could review and approve pediatric use labeling for products from different companies and coordinate implementation of labeling changes for similar agents.

With respect to effectiveness claims, pharmacokinetics, and safety data, much information is Drug specific and will be reviewed as it is submitted. Therefore, the agency is not adopting the comment's

suggestions. The agency advises, however, that, in general, when a class of Drug products is involved, FDA examines labeling as it applies to the class.

#### F. Impact on Industry

11. One comment claimed that the rule places NDA holders at a competitive disadvantage relative to abbreviated new Drug application (ANDA) holders. The comment stated that the rule would give NDA holders the burden and responsibility for pediatric studies and literature searches, but not impose a similar burden and responsibility on ANDA holders.

FDA disagrees with the comment in part. The rule is directed to anyone marketing a prescription Drug and is intended to encourage the inclusion of more complete information about use of a Drug in the pediatric population and about hazards associated with this use. The rule permits a new basis for reference to pediatric uses, but it does not impose a new requirement to conduct studies in pediatric populations. To the extent that NDA holders have access to data not available to ANDA holders, they will have more data to examine and more likelihood of having a basis for proposing changes to the "Pediatric use" subsection of labeling. The agency believes this represents only a modest burden and, in any event, sees no other way to gain further pediatric information in labeling. ANDA holders cannot be required to examine data they do not possess. ANDA holders are not precluded from providing pediatric use data, and are expected to do so under this rule, if data are available. An ANDA applicant who believes new safety or effectiveness information should be added to a product's labeling should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

#### G. Minor Editorial Changes

12. One comment said that labeling revisions that are editorial in nature and are used to reformat existing pediatric use labeling information to conform to the rule should be made in accordance with Sec. 314.70(d) (21 CFR 314.70(d)) (changes described in the annual report). The comment said that this would also facilitate the agency's processing of minor changes.

FDA agrees with the comment. As stated in the preamble to the proposed rule, "[m]inor editorial changes may be made in accordance with Sec. 314.70(d)" (57 FR 47423 at 47426). To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "pediatric population" or "pediatric patients." For products other than biological products, such changes are considered minor editorial changes.

As stated in the preamble to the proposed rule, for biological products, such changes are to be submitted in accordance with the procedures outlined in Sec. 601.12 (21 CFR 601.12) (57 FR 47423 at 47426).

#### H. Format of Proposed Labeling

13. One comment said that it is impractical and impossible to list on the labeling all dosages and hazards for the pediatric population. The comment suggested placement of a general label on all adult prescription drugs stating that the medication should not be given to pediatric patients without a physician's instructions. The comment said that requiring overly complicated and lengthy information on labeling would discourage the prescribing of needed medications.

FDA believes that the comment misinterprets the proposed rule and the purpose of pediatric use labeling. The purpose of the rule is to encourage more pediatric use information in labeling and to provide practitioners with more information on pediatric use.

14. One comment said that for certain products, e.g., corticosteroids, where class labeling has been in effect, the agency

will have to decide and communicate how the pediatric wording will be addressed.

In most cases, pediatric labeling will be Drug specific. Where class labeling exists, FDA generally examines the labeling for those products as a whole.

#### IV. Specific Comments on the Proposed Rule

##### A. Section 201.57(f)(9)(i)

FDA, on its own initiative, has added a definition in Sec. 201.57(f)(9)(i) to indicate that under paragraphs (f)(9)(ii) through (f)(9)(viii), the terms ``pediatric population(s)'' and ``pediatric patient(s)'' are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

##### B. Proposed Sec. 201.57 (f)(9)(i) and (f)(9)(ii)

FDA received no comments on these provisions (renumbered as Sec. 201.57(f)(9)(ii) and (f)(9)(iii)), and has finalized them without change.

##### C. Proposed Sec. 201.57(f)(9)(iii)

Proposed Sec. 201.57(f)(9)(iii) (renumbered as Sec. 201.57(f)(9)(iv)) states, in part, that ``FDA may approve a Drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drugs are sufficiently similar in children and adults to permit extrapolation from the adult data to children. The additional information supporting pediatric use must include data on the pharmacokinetics of the Drug in children for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the Drug in children, controlled or uncontrolled studies confirming the safety or effectiveness of the Drug in children, pertinent premarketing or postmarketing studies or experience, may be necessary to establish the applicability of the adult data to children.''

15. One comment said FDA should revise proposed Sec. 201.57(f)(9)(iii) to indicate that pharmacokinetic data are not mandatory in some situations. Another comment stated that pharmacokinetic data may not be the most appropriate way to determine pediatric dosing because the differences in metabolism or in distribution in pediatric patients may support dosing that will not necessarily be related to blood levels. Both comments stated that dosing for inhalation products should not be based on pharmacokinetics.

Another comment said that difficulties in obtaining informed consent, use of placebo controls, and obtaining adequate blood samples for pharmacokinetic analysis in pediatric patients are not serious impediments to performing studies necessary for appropriate pediatric labeling. The comment said there is a well-established ethical structure within which informed consent may be obtained and placebo controls used in the pediatric population, and that current technology requires only very small blood samples for measurement of most compounds. According to the comment, the primary impediments to doing adequate clinical trials in the pediatric population are the absence of a regulatory mandate and the existence of economic disincentives.

The agency recognizes that pharmacokinetic data are important sources of information, but may not always be the most appropriate method for determining pediatric dosing schedules and may be infeasible, unnecessary, or insufficient. Other types of data or experience may sometimes substitute for pharmacokinetic data, and other data or experience in the pediatric population may be needed in addition to pharmacokinetic data. The agency has modified the rule to state that the additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the Drug in the pediatric population for determination of pediatric dosage.

As discussed in response to comment 4 in section III.C. of this document, this rule does not create a new requirement for pediatric studies, but the authority for requiring pediatric studies already exists. There are situations in which data on safe and effective use in pediatric patients may be necessary for approval or for continued marketing of a Drug. Revised Sec. 201.57(f)(9) does not create the requirement for pediatric studies, but is intended to encourage the inclusion of more comprehensive labeling about pediatric use by permitting use of adult data in establishing pediatric efficacy. Specifically, the rule allows the pediatric use statement to be based on adequate and well-controlled studies in adults when additional information exists to show that the course of the disease and the effects of the Drug are sufficiently similar in adults and pediatric patients to permit extrapolation from the adult efficacy data to pediatric populations.

FDA has, on its own initiative, amended proposed Sec. 201.57(f)(9)(iii) to indicate that FDA's determination whether the effects of a Drug are sufficiently similar in adults and pediatric patients will include an examination of the Drug's beneficial and adverse effects. FDA has also amended Sec. 201.57(f)(9)(iii) to make clear that other information besides pharmacokinetic data may be necessary not simply to "establish the applicability of the adult data to pediatric patients," but, more generally, "to show that the Drug can be used safely and effectively in pediatric patients." Section 201.57(f)(9)(iii) has also been modified to remove any potential misimpression that uncontrolled studies could demonstrate effectiveness.

16. One comment questioned the rule's language about extrapolating adult data to pediatric patients. The comment said that the exact mechanism by which many psychiatric drugs work is not known, so that, for these Drug products, extrapolation between adult and pediatric populations may be inaccurate and potentially hazardous. The comment noted that randomized controlled studies of tricyclic antidepressants in pediatric patients have raised questions regarding efficacy, while safety issues have been raised based on noncontrolled data indicating a potential risk, which might not have been clear based on adult data, of sudden cardiac death in pediatric patients using tricyclics.

FDA agrees that extrapolation from adult experience is inappropriate, and thus unacceptable, in some cases. Extrapolation is not necessary under the rule, but is an alternative to the conduct of adequate and well-controlled studies in pediatric patients. In those cases where the pediatric use statement is based primarily on adequate and well-controlled studies in adults, additional information supporting pediatric use is usually needed, ordinarily including data on the pharmacokinetics of the Drug in the pediatric population for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the Drug in pediatric patients, data from other studies supporting the safety or effectiveness of the Drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the Drug can be used safely and effectively in the pediatric population.

17. One comment said that the preamble to the final regulation should clarify that "other information" supporting pediatric use in proposed Sec. 201.57(f)(9)(iii) need not be limited to data developed or sponsored by the NDA holder, but may include data such as reports of studies by academic researchers in peer-review journals that were prepared by persons who are not related to the NDA sponsor.

The agency believes that no change is needed in revised Sec. 201.57(f)(9)(iv) because the section does not suggest that the data must have been developed or sponsored by the NDA holder.

D. Proposed Sec. 201.57(f)(9)(iv)

FDA received no comments on this provision (renumbered as Sec. 201.57(f)(9)(v)), and has finalized it without change.

E. Proposed Sec. 201.57(f)(9)(v)

Proposed Sec. 201.57(f)(9)(v) (renumbered as Sec. 201.57(f)(9)(vi)) provides, in part, that "[i]f the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: 'Safety and effectiveness in children have not been established.'"

18. One comment expressed concern that this provision may create disincentives for sponsors to develop better information on pediatric use of their drugs. The comment suggested that FDA require mandatory phased-in safety testing and appropriate clinical studies of pharmaceuticals in the pediatric population. Alternatively, the comment recommended that FDA and manufacturers work to develop agreements whereby the manufacturer consents to carry out additional postapproval pediatric studies.

FDA believes that the comment suggests actions beyond the scope of this rule. FDA encourages pediatric testing, and, as discussed in comment 4 in section III.C. of this document, has the authority to require pediatric studies. In some cases, FDA will require pediatric studies for approval or continued marketing. This rule, however, does not add new requirements for pediatric studies, but rather describes the kind of data that can be used to support labeling claims.

F. Proposed Sec. 201.57(f)(9)(vi)

Proposed Sec. 201.57(f)(9)(vi) (renumbered as Sec. 201.57(f)(9)(vii)) provides "[i]f the sponsor believes that none of the statements described in paragraphs (f)(9)(i) through (f)(9)(v) (renumbered as (f)(9)(ii) through (f)(9)(vi)) of this section is appropriate or relevant to the labeling of a particular Drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement."

19. One comment asserted that the proposal did not adequately address the problem of a large number of drugs that have been approved and marketed for years without pediatric usage information in their labeling, which are widely used in pediatric patients and for which there is substantial published literature regarding their pediatric use. The comment noted that proposed Sec. 201.57(f)(9)(vi) would impose on the sponsor the responsibility for providing information that would promote the safe and effective use of prescription drugs in pediatric patients and noted that the sponsor may have complex reasons for not necessarily wanting to include pediatric information in the labeling. The comment recommended that the final rule include a mechanism that would allow summary information from authoritative published literature to be added to the labeling of currently marketed drugs so this information would be available to the pediatric prescriber. It suggested that the rule should provide an option permitting "recognized authoritative medical experts or groups of experts" to provide information to support pediatric information in the labeling in lieu of the sponsor.

Another comment urged the agency to provide for the incorporation of supplemental indications into Drug labeling based solely on information submitted by persons other than the sponsor. The comment said that changes should be made based on studies reported in peer-reviewed medical literature, rather than relying on submissions by the sponsor. The comment stated that this was necessary to make the labeling of certain drugs, particularly anticancer agents, conform to the current state of medical knowledge. The comment noted that FDA restricts promotion of off-label uses, and third-party payers often take the position that agents that have no labeled indication for treatment of cancers in pediatric patients are experimental and therefore nonreimbursable, even though they may be safe and effective.

The sponsor is primarily responsible for bringing forth evidence to support labeling changes. A third party could, however, provide evidence to persuade the agency to direct the sponsor to submit a labeling supplement. A study need not have been conducted by or on behalf of the sponsor in order to support a labeling change. The evidence to support labeling should continue to be of the type and

quality that would ordinarily support labeling statements. Published literature on pediatric use may contribute to this evidence, and authoritative groups may suggest approaches, but the views of authoritative groups do not themselves represent sufficient evidence of effectiveness. With respect to the comment concerning reimbursements, the agency advises that reimbursements to patients are beyond the scope of the rule and FDA authority. However, FDA agrees with the underlying concern that appropriate indications be on the label so that practitioners understand how best to prescribe the Drug for the patient's medical benefit.

G. Proposed Sec. 201.57(f)(9)(vii)

Proposed Sec. 201.57(f)(9)(vii) (renumbered as Sec. 201.57(f)(9)(viii)) states "[i]f the Drug product contains one or more excipients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk, generally in the 'Contraindications,' 'Warnings,' or 'Precautions' section, shall be made."

20. Four comments expressed concern about this proposed requirement. One comment said that the data relating to the toxicity of excipients, including preservatives, are inconclusive, making the requirement inappropriate. The comment stated that FDA should encourage collection and analysis of data to enable specific determinations on the use of excipients and preservatives.

Another comment asked FDA to clarify whether the proposed requirement that labeling contain statements about excipients that present an increased risk of adverse effects to the neonate or other pediatric subgroups was intended to reflect published literature or to be based on studies designed to show whether an increased risk exists. It added that it was not clear how or by whom a determination of increased risk would be established. The comment suggested that the final rule state that a sponsor can rely on existing information and is not required to conduct additional studies. The comment also suggested that, if additional studies were necessary, animal data be used rather than requiring clinical studies in neonates. It suggested that a standardized list could be developed jointly by industry and FDA.

A third comment suggested that a requirement that any labeling identify any increased risk of toxic effects to neonates or other pediatric groups should not be interpreted as establishing a requirement that sponsors conduct toxicology or other studies to identify or quantify such risks. The comment also stated that the preamble to the final regulation should state whether the increased risk of toxic effects is limited to those established by human data or experience, or would also include those based on animal or in vitro models.

A fourth comment noted that ANDA holders may use excipients different from those used by the reference listed Drug. The comment suggested that ANDA holders should be required to provide specific information regarding excipients used.

The final rule requires the labeling for a Drug product containing one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups to note such risks in the "Contraindications," "Warnings," or "Precautions" section of the labeling. If toxicity data for the inactive ingredient(s) do not exist or are inconclusive, revised Sec. 201.57(f)(9)(viii) would not require the labeling to contain a statement about an increased risk to neonates or other pediatric subgroups. However, in such cases, FDA encourages applicants to collect and analyze data on inactive ingredients and preservatives that could represent a pediatric risk. These data may include human data, animal data, or data derived from in vitro models.

FDA also notes that current regulations already require ANDA applicants whose inactive ingredients differ from those used in the reference listed Drug to identify and characterize the inactive ingredients in a proposed Drug product and to provide information demonstrating that such inactive ingredients do not affect the safety of the proposed Drug product (see 21 CFR 314.94(a)(9)). Given these

provisions, there is no reason to believe that the inactive ingredients used in a generic Drug product are any less safe than those in the reference listed Drug.

The agency has determined that, for the purposes of this final rule, the terms ``excipient'' and ``inactive ingredient'' have the same meaning. However, because the agency generally uses the term ``inactive ingredient,'' the agency has, on its own initiative, amended proposed Sec. 201.57(f)(9)(vii) to refer to ``inactive ingredients'' instead of ``excipients.''

#### V. Legal Authority

FDA's revision to the ``Pediatric use'' subsection of prescription Drug labeling is authorized by the Federal Food, Drug, and Cosmetic Act (the act) and by the Public Health Service Act (the PHS act). Section 502(a) of the act prohibits false or misleading labeling of drugs, including, under section 201(n) of the act, failure to reveal material facts relating to potential consequences under customary conditions of use.

Section 502(f) of the act requires Drug labeling to have adequate directions for use and adequate warnings against use by the pediatric population where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration, as are necessary to protect users.

Section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Drug products that do not meet the requirements of any paragraph of section 502 of the act are deemed to be misbranded.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that prescription Drug labeling provide the practitioner with adequate information to permit safe and effective use of the Drug product. Under section 505 of the act, FDA will approve an NDA only if the Drug is shown to be both safe and effective for its intended use under the conditions set forth in the Drug's labeling. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Under Sec. 201.100(d) (21 CFR 201.100(d)) of FDA's labeling regulations, prescription Drug products must bear labeling that contains adequate information under which licensed practitioners can use the Drug safely for their intended uses. Section 201.57 describes specific categories of information, including information for Drug use in selected subgroups of the general population, which must be present to meet the requirements of Sec. 201.100.

In addition, under 21 CFR 314.125, FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of part 201 (21 CFR part 201).

Section 351 of the PHS act provides legal authority for the agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that they meet standards ``designed to insure the continued safety, purity, and potency of such products'' prescribed in regulations (42 U.S.C. 262(d)). The ``potency'' of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription Drug products, including biological products.

A Drug product that is not in compliance with Sec. 201.57(f)(9) would be considered misbranded and an unapproved new Drug under the act. A noncomplying product that is a biological product would, in addition, be considered falsely labeled and an unlicensed biological product under the PHS act.

#### VI. Implementation

The primary purpose of the proposed rule was to revise the existing pediatric labeling requirements by expanding the basis on which

information about use of a Drug in the pediatric population may be included. The proposed rule would have required sponsors to comply with the pediatric use provisions 1 year after the date of publication of a final rule in the Federal Register.

21. Several comments said that the proposed 1-year implementation period was too short. The comments claimed that extrapolating and reviewing data would be time consuming and that the agency would be unable to approve pediatric use labeling within 1 year. The comments suggested that the agency cooperate with industry to establish a 3-year implementation schedule, only require sponsors to submit revised labeling in 1 year, or make the rule effective in 2 years.

The agency has carefully considered the comments and has revised the implementation schedule for the final rule. The agency will accept pediatric use information based on revised Sec. 201.57(f)(9) after January 12, 1995.

Sponsors have a continuing obligation to maintain labeling that is truthful and comprehensive in accordance with Sec. 201.57, including Sec. 201.57(f)(9). Section 201.57(f)(9) requires labeling to contain at least one of the statements under Sec. 201.57(f)(9)(ii) through (f)(9)(vi), or to propose an alternative statement under Sec. 201.57(f)(9)(vii). The statement must accurately describe available data.

Sponsors must, therefore, reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new Sec. 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and Drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under new Sec. 201.57(f)(9)(iv), and need not inform the agency of this conclusion.

Therefore, FDA expects sponsors to examine available information and update pediatric labeling for their products, if appropriate. Sponsors should also examine data on the extent and nature of use of their products in pediatric patients. If FDA concludes that a particular Drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric population, and the Drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric use information.

If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded Drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as well as an unapproved new Drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262).

Under the final rule, any new or revised pediatric indications, or statements on pediatric indications, or statements on pediatric use under the provisions of Sec. 201.57(f)(9)(ii) through (f)(9)(iv) would require FDA approval of a supplemental application in accordance with Sec. 314.70(b) or Sec. 601.12. Other changes to proposed Sec. 201.57(f)(9)(ii) through (f)(9)(iv) to add or strengthen precautions, contraindications, warnings, or adverse reactions or to add or strengthen dosage and administration instructions to increase a product's safety (for products other than biological products) could be put into effect at the time a supplement covering the change is submitted to FDA in accordance with Sec. 314.70(c). Minor editorial changes to products other than biological products may be made in accordance with Sec. 314.70(d).

To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "Pediatric population" or "pediatric patients." The agency advises that after January 12, 1995, such changes must be made, no later than the first time that labeling is sent to the printers or ordered for reprinting to



replenish old stocks of labeling. Such changes for products other than biological products are considered minor editorial changes and may be submitted in an annual report in accordance with Sec. 314.70(d).

Any new or revised statement under Sec. 201.57(f)(9)(viii) regarding inactive ingredients that may be toxic to the neonate or other pediatric subgroup should be made in accordance with the provisions of Sec. 314.70(c) or Sec. 601.12 (21 CFR 601.12), as appropriate.

All supplements containing pediatric use information and their mailing covers should be plainly marked ``Pediatric supplements.''

For those products subject to section 351 of the PHS act, labeling changes should be made in accordance with Sec. 601.12. Persons who have questions regarding such changes and need guidance on whether a supplement is necessary should contact one of the following three divisions as appropriate: Office of Therapeutics Research and Review, Division of Application Review and Policy (HFM-585), 301-594-5109; Office of Vaccine Research and Review, Division of Vaccine and Related Product Applications (HFM-475), 301-594-2090; or Office of Blood Research and Review, Division of Blood Applications (HFM-370), 301-594-2012; at the following address: Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852.

22. One comment suggested that the rule would have a substantial economic impact, particularly if the agency adheres to the proposed 1-year implementation period. The comment said that there are cost factors arising from the extensive resources required to reevaluate the available clinical study data and literature to extrapolate adult safety data to the pediatric age group or groups. The comment noted that Drug studies in pediatric patients have additional costs not experienced with the adult population, and may, in some cases, require inpatient studies. The comment also claimed that encouraging pediatric studies prior to approval or as a Phase 4 commitment could lengthen the development process, slow Drug approval, and thereby have an additional economic impact.

The agency has considered the comment and has revised the implementation schedule for this final rule. The implementation schedule is discussed in section VI. of this document.

The agency stresses that this rule does not require sponsors to conduct pediatric studies. The authority to require studies is found in the act and regulations already promulgated. Rather, this rule recognizes alternative methods of establishing substantial evidence to support pediatric labeling claims. Where a finding of substantial evidence to support a pediatric indication or a pediatric use statement has not been met for a specific subgroup or for any pediatric population, the sponsor must instead indicate that no data are available. If a sponsor believes that a pediatric use statement would be inappropriate or irrelevant to the labeling of a particular Drug, it must provide a reason for omitting the statement. This rule does not affect any determination by the agency that pediatric studies are needed before or after approval for a new Drug.

## VII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VIII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that

this final rule is consistent with the principles set out in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule does not impose additional requirements for sponsors to conduct pediatric studies, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

#### List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

#### PART 201--LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530-542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.57 is amended by revising paragraph (f)(9) to read as follows:

Sec. 201.57 Specific requirements on content and format of labeling for human prescription drugs.

\* \* \* \* \*

(f) \* \* \*

(9) Pediatric use:

(i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms ``pediatric population(s)'' and ``pediatric patient(s)'' are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the ``Indications and Usage'' section of the labeling, and appropriate pediatric dosage information shall be given under the ``Dosage and Administration'' section of the labeling. The ``Pediatric use'' subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the Drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the Drug, and other information related to the safe and effective pediatric use of the Drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the ``Clinical Pharmacology'' or ``Clinical Studies'' section. As appropriate, this information shall also be contained in the ``Contraindications,'' ``Warnings,'' and elsewhere in the ``Precautions'' sections.

(iii) If there are specific statements on pediatric use of the Drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the ``Pediatric use'' subsection of the labeling and discussed in more detail, if appropriate, under the ``Clinical Pharmacology'' and ``Clinical Studies'' sections. Appropriate pediatric dosage shall be given under the ``Dosage and Administration'' section

of the labeling. The ``Pediatric use'' subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the Drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the Drug, and other information related to the safe and effective pediatric use of the Drug. As appropriate, this information shall also be contained in the ``Contraindications,'' ``Warnings,'' and elsewhere in the ``Precautions'' sections.

(iv) FDA may approve a Drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the Drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the Drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the Drug in the pediatric population, data from other studies supporting the safety or effectiveness of the Drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the Drug can be used safely and effectively in pediatric patients. When a Drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ``Pediatric use'' subsection of the labeling shall contain either the following statement, or a reasonable alternative: ``The safety and effectiveness of (Drug name) have been established in the age groups -- to -- (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (Drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (Drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).'' Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the ``Clinical Pharmacology'' or the ``Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ``Clinical Pharmacology'' section. Pediatric dosing instructions shall be included in the ``Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the Drug in pediatric patients shall be cited briefly in the ``Pediatric use'' subsection and, as appropriate, in the ``Contraindications,'' ``Warnings,'' ``Precautions,'' and ``Dosage and Administration'' sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the ``Pediatric use'' subsection of the labeling shall contain an appropriate statement such as ``Safety and effectiveness in pediatric patients below the age of (--) have not been established.'' If use of the Drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ``Contraindications'' or ``Warnings'' section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: ``Safety and effectiveness in pediatric patients have not been established.'' If use of the Drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ``Contraindications'' or ``Warnings'' section of the

labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular Drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the Drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the Drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the ``Contraindications,'' ``Warnings,'' or ``Precautions'' section.

\* \* \* \* \*

Dated: November 15, 1994.

David A. Kessler,  
Commissioner of Food and Drugs.  
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